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Evaluation of the glycemic effect of methotrexate in psoriatic arthritis patients with metabolic syndrome: A pilot study

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Abstract

Methotrexate (MTX) is a systemic immunosuppressant drug used for the treatment of psoriasis and psoriatic arthritis. Previous studies demonstrated a potential association between psoriasis and diabetes mellitus, obesity, atherosclerosis, hypertension, eventuating into metabolic syndrome. This study aimed at exploring the glycemic effects of MTX in psoriatic arthritis (PsA) patients. In this prospective cross-sectional study, 27 patients with PsA were evaluated. The status of PsA and presence of accompanying metabolic syndrome was determined by standard criteria and indices. Blood indicators including HbA1c, erythrocyte sedimentation rate, fasting blood sugar, total cholesterol, high-density lipoprotein, triglycerides, and C-reactive protein were examined before and 12 weeks after MTX therapy. There were no significant changes between HbA1c levels before and after MTX therapy in both genders (men: P=0.131, women: P=0.803). In addition, HbA1c levels in PsA patients with metabolic syndrome were not different before and after treatment (P=0.250). Finally, HbA1c levels did not change in PsA patients without metabolic syndrome before and after therapy (P=0.506). MTX in PsA patients does not appear to have hyperglycaemic effects in the short-term and can be safely used in patients with metabolic syndrome and diabetes.

Introduction

Psoriasis (PsO) is defined as a systemic, inflammatory dermatologic disease which affects approximately 2-3% of the global population.[1,2] Furthermore, psoriatic arthritis (PsA) can develop in 7-48% of all PsO subjects.[3,4] Patients with PsO and/or PsA are at a higher risk for development of other chronic pathologic diseases, which can complicate the management of these patients.[5-7] Previous studies have proved that metabolic syndrome is related to a state of chronic low-grade inflammation.[8,9] The underlying mechanism is partially unknown, but a group of cytokines, including tumor necrosis factor-α (TNF-α), have been evidenced to reduce the activity of insulin, contributing to insulin resistance.[9-11] Unfortunately, there is limited data on association between metabolic syndrome and rheumatological disorders, even though a

few studies have reported an increased incidence of metabolic syndrome in patients with rheumatologic disease.[12-14] Besides, a few previous studies have indicated that there is an association between the metabolic syndrome and PsO.[15,16] Additionally, epidemiological evidence has proposed that systemic anti-inflammatory therapy might be helpful to decrease the risk of cardiovascular disease (CVD) in patients suffering from psoriasis.[17,18] Methotrexate (MTX) is an anti-rheumatic drug with its cytotoxic, anti-inflammatory and immune modulatory activities often used in psoriasis treatment. However, despite its use for the last 60 years, a close evaluation of its adverse effects and related risk factors has not been performed.[19] In spite of growing concerns about cumulative toxicity, there are no detailed data for complications associated with an increased cumulative dose of MTX.[20] Studies have demonstrated significant reductions in CVD-related mortality in patients treated with methotrexate.[21] This finding has been attributed to the potent anti-inflammatory properties of methotrexate.[21,22] The aim of this study was to explore the effects of short-term methotrexate therapy on the blood levels of glucose and HbA1c in patients having psoriasis.

Materials and Methods

Subjects

In this multicenter cross-sectional study, 27 patients (aged 30-60 years) with PsA from February 2016 to February 2018 were enrolled. The evaluation subjects included the evidence of lifestyle factors including smoking behavior, medical history, taking medications, presence of diabetes mellitus, hypertension, duration of disease, comorbidities, and clinical examinations which were obtained to discover the presence of PsA. Also, physical examination included recording the number of tender and swollen joints. To confirm the suspect of PsA we also performed joints radiogram and enthesis sonography. The diagnosis of PsA was established by standard criteria for psoriatic arthritis (CASPAR) with a score >3 points.[18] Additionally, other parameters such as weight, height and waist circumference, body mass index (BMI) (kg/m^2) and blood pressure were also measured. The status of PsA was determined by the following standard indexes: the Bath Ankylosing Spondylitis Disease Activity Index,[23] Disease Activity Score 28[24] and the health assessment questionnaire.[25] Furthermore metabolic syndrome was determined via the International Diabetes Federation (IDF) 2004 and the National Cholesterol Education Program Adult Panel III (NCEP ATP III) (NCEP ATP III) 2001.[26,27] All patients were treated with oral methotrexate (7.5 mg/kg) weekly for three months. Before the collection of samples a written informed consent was obtained from each participant and ethical approval was granted by the ethics committee of the Mazandaran University of Medical Sciences, Pardis Unit, Ramsar, Iran.

Inclusion and exclusion criteria

In this study, PsA was diagnosed and confirmed by expert rheumatologists based on the CASPAR.[28] Subjects with other inflammatory rheumatic diseases, myocardial infarction (MI), stroke, hyper-glycaemic status different from diabetes mellitus type 2 *e.g.* hyperthyroidism and hyperglicaemic, renal insufficiency, lung or liver or retroperitoneal fibrosis as well as patients who took anti-inflammatory drugs (NSAIDs or corticosteroids) were excluded from the study.

Blood analysis

Following serum sampling, they were kept at -80ºC until further processing. The HbA1c and erythrocyte sedimentation rate were primarily measured. Also, the serum concentrations of fasting blood sugar (FBS), total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerides and C-reactive protein were measured using an automated analyzer (Model 912, Hitachi, Japan). All these parameters were examined before and after 12 weeks of treatment with methotrexate.

Statistical analysis

Data was expressed as mean ± standard deviation (SD). Statistical analysis was conducted using SPSS version 18 (SPSS, Inc, Chicago, IL, USA). Differences were evaluated with the paired t test and chi-square test. The normality of data was checked using the one-sample Kolmogorov–Smirnov Test. The significant level of differences was set at 0.05.

Results

Inclusion criteria were met by 35 patients. Among these, 27 patients continued the study with the mean age of 43.22±8.9. Nine (33.33%) patients were female and 18 (66.66%) were male. Demographic data and clinical features of patients before and after treatment are shown in Table 1. Hyperlipidemia was present in 7 (25.93%) patients at baseline for

Table 1. Demographic and clinical features of the study patients.

Variation	Patients with PsA before treatment n=27	Patients with PsA after treatment n=27	P value
Age (years)	43.22±8.9	-	-
Gender			
Men N (%)	18 (66.7)	-	-
Women N (%)	9 (33.3)	-	-
History of diabetes N (%)	2 (10.0)	-	-
History of stroke N (%)	10 (35.0)	-	-
History of Hyperlipidemia N (%)	7 (20.0)	-	-
FBS (mg/dL)	103.2±30.2	101.3±22.8	0624
Total cholesterol (mg/dL)	165.7±26.9	166.5±33.2	0.881
HDL (mg/dL)	39.6±7.7	42.8±6.2	0.005
LDL (mg/dL)	98.7±22.7	104.6±22.7	0.059
CRP	100% negative	100% negative	0.21
ESR (mm/hour)	24.2±17.9	23.5±17.6	0.722

PsA, psoriatic arthritis patients; FBS, fasting blood sugar; HDL, high-density lipoprotein cholesterol; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

which 5 (18.52%) patients were using medications. Family history of stroke was present in 10 (37%) patients. In this study, 7 (25.93%) patients had a normal weight, 10 (37%) patients were overweight, and the other 10 patients were obese. HbA1c test was taken before and after using methotrexate. At baseline, 2 (7.41%) patients had diabetes while the rest were negative. There were no significant differences between HbA1c levels among genders before and after treatment with methotrexate (men: P=0.131, women: P=0.803) (Figure 1). According to the NCEP, 20 (74.04%) patients had the signs of metabolic syndrome while the other 7 (25.93%) did not. However, according to IDF, 19 (70.37%) patients showed the signs of metabolic syndrome and 8 (29.63%) patients didn't. Furthermore, based on the NCEP index, HbA1c levels in PsA patients with metabolic syndrome were 5.7±0.9% before and 5.9±0.9% after methotrexate therapy (P=0.250). However, HbA1c levels in PsA patients without metabolic syndrome were 5.6±0.4 % and 5.7±0.5% before and after methotrexate therapy respectively (P=0.506) (Figure 2).

Discussion

Several studies have proposed that patients with PsA are at increased risk of CVD, obesity, diabetes and fatty liver disease.[29-31]Additionally, previous reports have indicated that HbA1c as the primary screening tool for glucose intolerance and the major predictive factor for cardiovascular events.[32,33] In the present study, we prospectively examined the influence of short-term anti-psoriatic therapy with methotrexate on HbA1c.The findings showed that there was no significant alteration in the HbA1c levels after 12 weeks of continuous treatment. Previously, deRotte and Perdan-Pirkmajer *et al.* demonstrated that MTX reduced HbA1c concentrations in patients with RA or PsA.[33,34] However, in a retrospective cohort study, Wu *et al.* showed that PsO, PsA, and RA patients under treatment with TNF inhibitors associated with MTX displayed no significant differences in terms of the HbA1c level.[35] Solomon *et al.* reported that there is a non-significantly lower risk of incident diabetes mellitus within patients suffering from PsA, PsO, or RA who were treated with methotrexate without tumor necrosis factor inhibitors or hydroxychloroquine. Nonetheless, in contrast to our study, Solomon *et al.* did not determine levels of HbA1C and FBS in their research.[36] Furthermore, Gisondi *et al.* conducted a survey of two groups of psoriasis patients who were newly treated with methotrexate and demonstrated that there was no detected changes in the FBS level.[37] In a 24-week retrospective study comparing TNF inhibitor, efalizumab, and methotrexate there was no significant alterations in FBS in any of the groups.[38] Cuchacovich *et al.* examined 37 patients with RA treated with methotrexate (mean 34.7 months), and found no significant changes have been in FBS.[39] All these reports are consistent with the results of our study. It appears that the administration of methotrexate for treatment of PsA does not have hyperglycaemic effects and thus it can be used in PsA patients with metabolic syndrome and diabetes. Moreover, the most important part of controlling the chronic disorders is following a healthy lifestyle along with proper medication. In addition, regular screening of diabetes by monitoring BMI, FBS levels, blood pressure and cholesterol levels may help early detection and management of new-onset diabetes in PsA patients being treated with methotrexate.

Conclusions

To conclude, the use of methotrexate was not related to a significant alteration in HbA1C or FBS levels in patients with PsA. According to the data obtained in this study, methotrexate can be used in the treatment of PsA patients without the risk of developing diabetes.

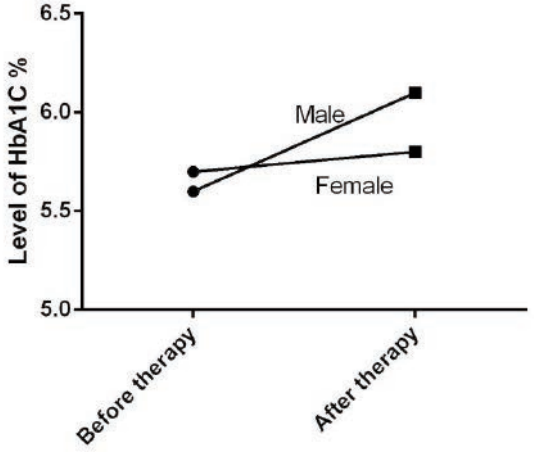

Figure 1. The level of HbA1c based on the gender of psoriatic arthritis patients. The results are presented as mean ± SEM. Statistically significant differences between control and patients (P<0.05).

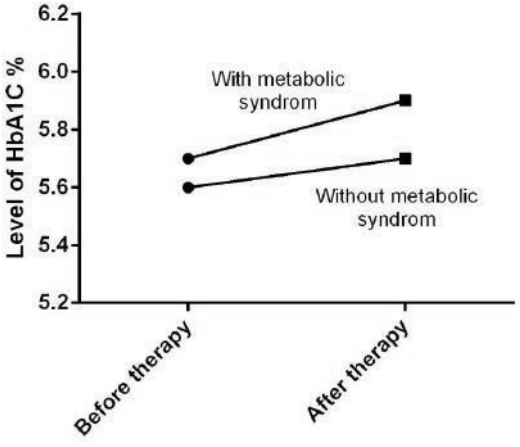

Figure 2. The level of HbA1c based on the National Cholesterol Education Program Adult Panel index in psoriatic arthritis patients patients with and without metabolic syndrome. Results are presented as mean ± SEM. Statistically significant differences between control and patients (P<0.05).

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